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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,392	08/03/2006	Laszlo Takacs	NU-BI-659XX	8285

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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,392	TAKACS ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-23 and 25-29* is/are pending in the application.

4a) Of the above claim(s) *3,4,7-16,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 6, 17, 18, 21-23 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-15, 17-23, and 25-29 are pending in the instant application; claims 3, 4, 7-16, 19 and 20, are withdrawn; claims 1, 2, 5, 6, 17, 18, 21-23 and 25-29 are the subject of the Office Action below.

Claim Rejections - 35 USC § 112 – Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 27-29, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite for reciting the phrase "wherein said complex analyte is enriched in a *specific* class of analyte elements" because one of ordinary skill in the art would not reasonably be able to determine the metes and bounds of this limitation. It is not how one of ordinary skill in the art would distinguish between analytes that are specific from those that are supposedly not specific.

Claims 27-29 are indefinite for reciting the phrase "numeric complexity" because one of ordinary skill in the art could not reasonably determine the metes and bounds of this limitation. The phrase does not appear to be an art-accepted phrase, nor is a proper definition set forth in Applicants' specification. It is unclear how one would calculate "numerical complexity" based on the lack of description from Applicants.

Claim 29 is indefinite for reciting the phrase "and represents 50% of the total mass of proteins of said sample" because it is not clear *what* represents 50% of the total mass. If Applicants intend for the "abundant proteins" to represent 50% of the sample, alternative wording is suggested because the sample has already been depleted of abundant proteins.

Claim 29 is indefinite for reciting "the total mass of proteins of said sample" because there is insufficient antecedent basis. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 17, 25 and 29 are anticipated by Conze:

Claims 1, 2, 17, 25 and 29, are rejected under 35 U.S.C. 102(a)/(b) as being anticipated by Conze *et al.*, *Ann. N.Y. Acad. Sci.*, *996*:222-226 (**2003**).

The claimed invention is generally directed towards a first step of generating a monoclonal antibody library from a complex analyte, followed by subtractive or differential screening. Specifically, amended claim 1 is directed towards a method of biomarker discovery, said method comprising the steps of:

providing a complex analyte as a candidate biomarker source said complex analyte being depleted of abundant proteins; providing a control sample for said complex analyte;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte as an immunogen to generate, from individual hyrbridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte; screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a statistically significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the antigens selectively bound by said at least one selected monoclonal antibody are said biomarkers.

Conze teaches the production of monoclonal antibodies from hybridoma cell lines towards CDCP1, a transmembrane protein that contains three CUB domains within the extracellular region and a hexalysine stretch within the cytoplasmic region, and is an important biomarker because it is highly expressed in lung and colon tumors. Conze teaches to analyze CDCP1 protein expression, monoclonal antibodies against the extracellular domain of CDCP1 were raised with CDCP1 being overexpressed in NIH-3T3 cells. Balb/c mice were then immunized with the resultant cell line NIH-3T3/huCDCP1 (*i.e.*, a complex analyte). After fusion of SP2/0 cells with immune spleen cells, hybridoma clones were selected that secreted antibodies reacting with NIH-3T3/huCDCP1 cells but not with parental cells (i.e., comparing the population against a control – the differential screening). Conze teaches that four antibodies (CUB1-CUB4) were obtained that fulfilled these criteria. Screening of peripheral blood cells revealed that the antibodies did not recognize mature lymphocytes, monocytes, granulocytes, erythrocytes, or platelets (*i.e.*, screening the population against another complex analyte). In contrast, multi-color analyses revealed that CDCP1 protein is almost exclusively expressed on a subset of CD34(+) stem/progenitor cells in bone marrow. Transplantation of purified CDCP1(+) cells into NOD/SCID mice resulted in engraftment of human cells with multi-lineage differentiation potential, suggesting that CDCP1 is a novel marker for hematopoietic stem cells. Conze notes that four antibodies were obtained that exhibited a "statistically significant" difference in binding to an antigen compared to the control sample (see page 225, first two paragraphs). Note: Applicants claimed method does not require that the sample first have abundant proteins, and then have a step that removes abundant proteins – only that the sample be free of abundant proteins, such as those from other cells of plasma (*i.e.*, "being depleted" is a state). This teaching also meets the limitation of claim 2 wherein there is an increase in the binding. As in claim 17, the complex analyte of Conze is effectively enriched by presentation in the genetically engineered cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5, 6, 17, 18, 21-23 and 25-29, are obvious in view of Conze, Stroobant, Hoogenboom, Andersen, and Nagai:

Claim 1, 2, 5, 6, 17, 18, 21-23 and 25-29, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Conze *et al.*, *Ann. N.Y. Acad. Sci.*, *996*:222-226 (**2003**), in view of Stroobant, U.S. Patent No. 7,208,268, issued on April 24, 2007, Hoogenboom *et al.*, *Immunotechnology*, *4*:1-20 (**1998**), Hoogenboom *et al.*, *Immunotechnology*, *4*:1-20 (**1998**), Andersen *et al.*, *PNAS*, *93*:1820-1824 (**1996**); and Nagai *et al.*, *Biochemical Society Transactions, 31(part 6)*:1438-1440 (**2003**).

The claimed invention is generally directed towards a first step of generating a monoclonal antibody library from a complex analyte, followed by subtractive or differential screening.

Specifically, amended claim 1 is directed towards a method of biomarker discovery, said method comprising the steps of:

providing a complex analyte as a candidate biomarker source said complex analyte being depleted of abundant proteins; providing a control sample for said complex analyte;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte as an immunogen to generate, from individual hyrbridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte; screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a statistically significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the antigens selectively bound by said at least one selected monoclonal antibody are said biomarkers.

Conze teaches the production of monoclonal antibodies from hybridoma cell lines towards CDCP1, a transmembrane protein that contains three CUB domains within the extracellular region and a hexalysine stretch within the cytoplasmic region. CDCP1 mRNA is highly expressed in lung and colon tumors and in the erythroleukemic cell line K562. Conze teaches to analyze CDCP1 protein expression, monoclonal antibodies against the extracellular domain of CDCP1 were raised with CDCP1 being overexpressed in NIH-3T3 cells (*i.e.*, a complex analyte). Balb/c mice were then immunized with the resultant cell line NIH-3T3/huCDCP1. After fusion of SP2/0 cells with immune spleen cells, hybridoma clones were selected that secreted antibodies reacting with NIH-3T3/huCDCP1 cells but not with parental cells (i.e., comparing the population against a control). Conze teaches that four antibodies (CUB1-CUB4) were obtained that fulfilled these criteria. Screening of peripheral blood cells revealed that the antibodies did not recognize mature lymphocytes, monocytes, granulocytes, erythrocytes, or platelets (i.e., screening the population against another complex analyte). In contrast, multi-color analyses revealed that CDCP1 protein is almost exclusively expressed on a subset of CD34(+) stem/progenitor cells in bone marrow. Transplantation of purified CDCP1(+) cells into NOD/SCID mice resulted in engraftment of human cells with multi-lineage differentiation potential, suggesting that CDCP1 is a novel marker for hematopoietic stem cells. Conze notes that four antibodies were obtained that exhibited a "statistically significant" difference in binding to an antigen compared to the control sample (see page 225, first two paragraphs). Note: Applicants claimed method does not require that the sample first have abundant proteins, and then have a step that removes abundant proteins – only that the sample be

free of abundant proteins, such as those from other cells of plasma (*i.e.*, "being depleted" is a state).

Although Conze a differential approach to comparing cells that express the antigen which hybridoma raised antibodies target, Conze does not explicitly teach a step of depleting abundant proteins from the sample, or that the sample is clinical of from a human body fluid.

Stroobant teaches methods for isolation and quantitation of proteins and other biomolecules differing between samples over a wide range of relative abundance. The invention provides for the identification of proteins as known species, or as species with novel sequence or novel post-translational modifications, and supplies a means for characterization and isolation of specific affinity reagents against such proteins. As in claim 5, Stroobant teaches the importance of depleting abundant proteins from the sample because of the diminished analytical performance caused by abundant proteins (col. 9, lines 49-62). As in claims 6 and 7, Stroobant teaches a "complex biological sample" and indicates that the sample can come from a diseased human's blood (paragraph bridging cols. 3 and 4). As in claim 18, Strooband differentially compares healthy and diseased individuals expression patterns (col. 3, lines 5-15). As in claims 21 and 22, and the final step of claim 23, Stroobant identifies the biomarker (see Steps III and IV in cols. 16 and 17). As in claim 28, Stroobant teaches complex analytes from two or more patients, such as a healthy and diseased patient as noted above. As in claims 27 and 29, the numeric complexity of the sample of Stroobant is less than 5-10%.

Hoogenboom provides an in-depth review article that relates to the use of antibody-based phage display methods. Certain of these methods include the production of monoclonal antibodies using phage display:

> "One of the most successful applications of phage display has been the isolation of monoclonal antibodies from large phage antibody libraries (Fig. 3). We will discuss the three types of such phage libraries, immune, naive and synthetic antibody libraries."

Hoogenboom, page 4, col. 2, lines 5-10. See also the entire discussion in the section titled, Antibody libraries, beginning on page 4 through page 8.

As in step 3 of claim 1, Hoogenboom also teaches certain methods for preparing a host of antibodies from a response to a complex antigens (page 10, section titled, *Selection on complex*

antigens). Hoogenboom also teaches subtractive methods for selecting antibodies (i.e., differential screening), wherein a control sample and another antigen sample are compared, such as normal cells vs. diseased cells (page 12, section titled, *Selection on cells*; see also Figure 4F on page 9, and description thereof; see also section titled, *Finding new antigens with phage antibody libraries*, on page 13). As in claim 21, the identity of the biomarker is determined (page 14, col. 1)

Hoogenboom provides an in-depth review article that relates to the use of antibody-based phage display methods. Certain of these methods include the production of monoclonal antibodies using phage display:

> "One of the most successful applications of phage display has been the isolation of monoclonal antibodies from large phage antibody libraries (Fig. 3). We will discuss the three types of such phage libraries, immune, naive and synthetic antibody libraries."

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As in step 3 of claim 1, Hoogenboom also teaches certain methods for preparing a host of antibodies from a response to a complex antigens (page 10, section titled, *Selection on complex antigens*). Hoogenboom also teaches subtractive methods for selecting antibodies (i.e., differential screening), wherein a control sample and another antigen sample are compared, such as normal cells vs. diseased cells (page 12, section titled, *Selection on cells*; see also Figure 4F on page 9, and description thereof; see also section titled, *Finding new antigens with phage antibody libraries*, on page 13). As in claim 21, the identity of the biomarker is determined (page 14, col. 1)

Andersen is directed towards the production of a recombinant antibody library from a complex antigen, wherein a host of antibodies are produced from the in vivo introduction of a complex antigen, and improved with phage display of Fab fragments. As in claim 5, the complex analyte of Andersen is fractionated; and as in claim 17 that the complex analyte is purified from other cell components (page 1820, section titled, *MHC Purification*). As in claim 6, Andersen teaches that the use of the complex antigen for generating the antibodies would have clinical use (see page 1824, col. 1, last paragraph).

Nagai teaches a method for preparing a library of monoclonal antibodies and its use for differentiating between cell types and control cells as well as cellular functions related to the display of the antigens that the antibody library is directed (see pages 1439-1440). Nagai also teaches identifying the biomarker (see page 1440).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the references is directed toward the use of highly selective antibodies for identifying and/or targeting particular antigens. One of ordinary skill in the art would have recognized the advantages of extending the method of Conze to broader and more comprehensive differential screening approaches, such as those of Hoogenboom, Stroobant, and the further techniques and characterizations of Andersen and Nagai. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Primary Examiner, Art Unit 1639